Treatment of Malignant Endocrine Pancreatic Tumors with a New Long-Acting Somatostatin Analogue, SMS 201-995

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Ten patients with malignant endocrine pancreatic tumors were treated with SMS 201-995 at doses of 50 μg twice daily, administered subcutaneously. Four out of 10 patients (40%)—1 patient with the Zollinger–Ellison syndrome and 3 of 6 with the watery diarrhea syndrome—responded objectively with more than 50% reduction of peptide levels, with a median duration of 15.5 months. All four patients improved symptomatically, with decreasing dyspeptic symptoms and decreasing diarrhoea. Three additional patients had a clear relief of symptoms without an effect on tumor-secreted peptides. The disease progressed in three patients during treatment. No reduction of tumor mass was seen in any of the patients. The main side effect noted was a slight but maintained increase in fasting blood glucose in four patients. In conclusion, SMS 201-995 had a beneficial effect in more than half of the patients and seems to be a valuable adjunct to other causal therapy in this patient category, especially in acute situations and weak patients because of its very few side effects.

Key words: Endocrine pancreatic tumors, malignant; somatostatin analogue SMS 201-995; tumor therapy

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Somatostatin is a naturally occurring peptide with a wide distribution in the body.

Because of its inhibitory effects, native somatostatin has been used therapeutically in various hypersecretory conditions in the gastrointestinal tract. In 1983 we could demonstrate the inhibition of tumor-secreted insulin and gastrin in a benign insulinoma and malignant gastrinoma (1). One disadvantage with native somatostatin is its short plasma half-life, only 2–3 min, which necessitates intravenous infusion (2). Another problem is the rebound phenomenon that occurs when the infusion is stopped (3).

A new long-acting somatostatin analogue, a cyclic octapeptide, SMS 201-995 (Sandoz, Basel, Switzerland) has recently become available (4). It is more resistant to enzymatic degradation than the native compound, and its plasma half-life when given intravenously is approximately 60 min (5). It can also be administered subcutaneously, and its plasma half-life is then approximately 2 h (5). SMS 201-995 has been shown to be much more potent than the native compound, and it selectively suppresses growth hormone (GH) and glucagon levels more than insulin levels (5).

There are reports of beneficial effects of SMS 201-995 in cases of malignant endocrine pancreatic tumors (6–13), but the experience is still very limited. We thus want to report the effect of this long-acting somatostatin analogue in the management of 10 patients with malignant endocrine pancreatic tumors.

SUBJECTS AND METHODS

Patients

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Methods

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SUBJECTS AND METHODS

Patients

Ten patients, eight men and two women, with a mean age of 64.7 years (range, 54–73 years) were included in the study. Most of the patients had tumors with multiple peptide secretion, but the peptide considered to be causing the clinical syndrome was called the 'main' tumor marker. One patient had the Zollinger–Ellison syndrome, whereas six had the watery diarrhea (WDHA) syndrome. One patient had a malignant insulinoma, and the other two had non-functioning tumors—that is, they had no specific hormone-related symptoms. Two patients with the WDHA syndrome had a MEN-1 trait. Seven patients had a remaining pancreatic tumor, and eight had liver metastases. One patient had lung metastases.

Five patients had been subjected to pancreatic surgery. Embolization of liver metastases had been undertaken in one case. Seven patients had received chemotherapy, mainly streptozocin plus 5-fluorouracil or doxorubicin (Adriamycin®), with initial responses but then failure of this treatment. These seven patients had also been treated with human leukocyte interferon with responses of various duration but were showing progressive disease when SMS 201-995 was started. Two patients had received no prior treatment, and therapy with SMS 201-995 was started because of their poor general condition, which made chemotherapy and interferon treatment impossible.

Methods

Fasting peripheral blood samples were collected before and during SMS therapy. Serum insulin, proinsulin, c-peptide, gastrin (14), human chorionic gonadotropin (HCG) alpha and beta subunits (15), pancreatic polypeptide (PP) (16), calcitonin (17), plasma vasoactive intestinal polypeptide (VIP) (18), glucagon (19), somatostatin (20), and neurotensin (21) were analyzed by radioimmunoassays described earlier. Routine hematology, liver enzymes, blood glucose, serum T_4, and thyroid-stimulating hormone (TSH) assays were checked before and regularly during treatment. Histophathologic diagnosis was established in all 10 cases on tissue specimens taken at surgery or by coarse-needle biopsy (22). All tumors were agyrophil with the Grimelius silver nitrate stain (23). Routinely fixed, paraffin-embedded sections were immunohistochemically investigated with antibodies against gastrin, insulin, PP, glucagon, somatostatin, HCG alpha, HCG beta, calcitonin, VIP, and neurotensin (24).

SMS 201-995

SMS 201-995, the long-acting cyclic octapeptide produced by Sandoz, was administered as daily subcutaneous injections at initial doses of 50 µg twice daily. In seven of the patients increased doses were required.

Evaluation of tumor response

In the evaluation of the therapeutic effect, *objective response* was defined as a reduction of the 'main' tumor markers and/or tumor size by >50%. *Stable disease* was defined as a reduction of the main tumor marker and/or tumor mass by <50% and no appearance of new metastases. *Progressive disease* was defined as an increase in tumor markers and/or tumor mass by >25% or appearance of new metastases.

RESULTS

Objective responses were seen in 4 of 10 patients (40%) treated with SMS 201-995 (Table I). The mean duration of the response was 13.5 months (median, 15.5 months; range, 5–18 months). All four patients had a reduction of the main tumor marker by more than 50% (one patient with the Zollinger–Ellison syndrome and three of six with the WDHA syndrome). No patient had a reduction of tumor mass. However, tumor size remained unchanged on computed tomography (CT) scans in all patients during the observation time (mean, 9 months). Three patients had stable disease with a mean duration of 4.3 months. In three of the patients with objective response and in two of the patients with stable disease the somatostatin dose was increased up to 200 µg/day within 2–14 months to maintain the effect. Progressive disease was noted in the other three patients.

Symptomatically, 7 of the 10 patients (70%)

Table I. Patients with malignant endocrine pancreatic tumors treated with SMS 201-995

Patient no.	Clinical syndrome*	Earlier treatment†	Duration of disease	SMS treatment: hormone levels‡		Duration of therapy	Duration of objective response	Sympt. effect	Adverse effect
				Before	After				
1	Z–E	CT; IFN	120 mo	Gastrin, 194 pmol/l	35.3 pmol/l	18 mo	18 mo	+	Slight diabetes
2	WDHA	CT; IFN	32 mo	No measurable marker		6 mo	—	+	Abd. pain + fever
3	WDHA	CT; IFN	38 mo	Calc, 18,000 ng/l	9000 ng/l	16 mo	16 mo	+	Higher insulin dose
4	Non-f	None	120 mo	Calc, 420 ng/l	660 ng/l	19 mo	—	+	Slight diabetes
5	WDHA	CT; IFN	84 mo	PP, 14.2 ng/l	7.0 ng/l	5 mo	5 mo	+	Slight diabetes
6	WDHA	CT; IFN	156 mo	Calc, 470 ng/l	180 ng/l	15 mo	15 mo	+	Slight diabetes, hypocalcemia
7	WDHA	None	4 mo	VIP, 190 pmol/l	190 pmol/l	2 mo	—	—	—
8	Hypoglycemia	None	2 mo	Insulin, 129 mU/l	102 mU/l	2 days	—	—	Lower b-glucose
9	Non-f	CT; IFN	36 mo	PP, 1.85 ng/ml	2.7 ng/ml	1 mo	—	—	—
10	WDHA	CT; IFN	76 mo	VIP, 37.6	73.8	6 mo	—	+	Abd. pain + fever

* Z–E = Zollinger–Ellison; WDHA = water diarrhea hypokalemia achlorhydria; non-f = non-functioning tumor.
† CT = chemotherapy; IFN = human leukocyte interferon.
‡ Calc = calcitonin; PP = pancreatic polypeptide; VIP = vasoactive intestinal polypeptide.

improved. As is shown in Table I, five patients with the WDHA syndrome, one with the Zollinger–Ellison syndrome, and one with a non-functioning tumor responded subjectively. One of the patients who did not respond had a VIPoma, which also produced large amounts of pancreatic somatostatin. In this case we attempted doses as high as 100 μg/h intravenously without achieving an effect.

In the four patients with objective response, all with multiple peptide secretion, the main marker peptide decreased, while the other peptides increased. There was a discrepancy in the inhibiting effect on the release of different peptides.

Another observation could be made in two patients (cases 3 and 4), whose tumors had no known production of gastrin. During treatment with SMS 201-995 serum gastrin levels increased in both, while the tumor markers decreased. Basal acid output was measured in one of them and was shown to be very low.

Adverse effects

The side effects with this somatostatin analogue are remarkably few. We noticed a slight increase in fasting blood glucose (1.8 ± 1.1 (SD) mmol/l) in 4 of the 10 patients (Table I). One patient with insulin-treated diabetes required a higher insulin dose. Another patient with a malignant insulinoma received SMS 201-995 during the first 24 h in hospital, but blood glucose levels rather *decreased*, and alternative treatment had to be initiated. No patient developed clinically significant diarrhea or steatorrhea, probably because we used a relatively low dosage and because eight patients received pancreatic enzymes prophylactically. The existence of a subclinical malabsorption or steatorrhea cannot be excluded, since fat excretion was not routinely measured. Two patients with the WDHA syndrome, both of whom had been subjected to extensive abdominal surgery (in one case by the method of Whipple), developed abdominal pain and fever attacks, which were interpreted as attacks of cholangitis. Decreased intestinal motility caused by the analogue could explain these attacks. In both patients SMS 201-995 was withdrawn, and in one the adverse symptoms decreased within 3 days, and SMS 201-995 could be reinitiated in a dose. Pain at the injection site was a patients who received higher doses.

One patient with MEN-1 and the drome was maintained on a low subs of calcium after surgery for hyperpa and developed severe hypocalcemia reference level, 2.20–2.60) 3 month tion of SMS, and vitamin D substitu was added. Parathyroid hormone (remained unchanged. The hypocal patient could reflect intestinal inhi dium absorption by the analog hormone or liver enzyme values or atology results were not altered by t

DISCUSSION

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One patient with MEN-1 and the WDHA syndrome was maintained on a low substitution dose of calcium after surgery for hyperparathyroidism and developed severe hypocalcemia (1.61 mmol/l; reference level, 2.20–2.60) 3 months after initiation of SMS, and vitamin D substitution therapy was added. Parathyroid hormone (PTH) levels remained unchanged. The hypocalcemia in this patient could reflect intestinal inhibition of calcium absorption by the analogue. Thyroid hormone or liver enzyme values or routine hematology results were not altered by the treatment.

DISCUSSION

The optimal treatment in malignant endocrine pancreatic tumors has not yet been established. Surgery is the primary form of treatment (25), but because most patients have inoperable metastasizing disease, other forms of therapy have to be considered. Chemotherapy produces objective responses in >60% of patients with malignant endocrine pancreatic tumors (EPT) with a median duration of response of 17 months (26). Human leukocyte interferon has recently been shown to give objective responses in 77% of patients with malignant EPT, with a median duration of 8.5 months (27). However, none of the treatments cure the disease, and alternative treatments are needed.

There are already several reports about the beneficial effects of SMS 201-995 in the treatment of malignant EPT. Improvement of symptoms, reduction of peptide levels, and, in isolated cases, reduction of tumor mass have been described (6–12).

In our study SMS 201-995 was attempted in 10 patients with advanced disease, in which both cytotoxics and interferon no longer had an effect. In two patients the somatostatin analogue was the only treatment that the patients could tolerate because of their poor clinical condition.

In more than half of our patients the treatment had a beneficial effect, with symptomatic and subjective responses in seven patients. In 4 out of 10 patients (40%) SMS 201-995 reduced the levels of tumor-produced peptides by more than 50%, with a median duration of 15.5 months. However, with time higher doses seemed to be required to keep the peptide levels down and clinical symptoms away. Six patients required a dose increase after 2–14 months of up to 200 μg/day. The patients seem to develop tachyphylaxis, which might be due to down-regulation of somatostatin receptors. In one patient with a somatostatin-producing VIPoma, 100 μg/h intravenously was tried without any effect. The therapy resistance in this particular case should be noted, since concomitant somatostatin production from a tumor probably down-regulates somatostatin receptors. This mechanism for therapy resistance to SMS 201-995 has not been reported earlier. The observation that symptomatic improvement persisted in spite of increasing peptide levels or occurred without accompanying decrease in tumor markers has also been made by others (12). This discrepancy between objective and symptomatic response could reflect the proportionally stronger and longer-lasting effect of SMS 201-995 on peripheral target organs—that is, the mucosa of the stomach and the intestine described in earlier reports (10). The increase in serum gastrin in two of our patients during treatment could also be an expression of this phenomenon. Decreased basal acid output was demonstrated in one of these two patients but not measured in the other.

Whether SMS 201-995 has an effect on tumor growth is still not known. In the present study no patient had a reduction of tumor mass. On the other hand, no increase in tumor size was seen on CT scan, which could indicate an inhibitory effect on tumor cell growth. In animal models, SMS 201-995 has been reported to have moderate but significant inhibitory effects on the growth of transplanted peptide-producing tumors (28). There have been reports in the literature about possible shrinkage of metastases of EPT during treatment with SMS 201-995 (13), but these observations need confirmation in additional studies of patients. Since SMS 201-995 does not excert cytostatic effects, the inhibited growth might be due to inhibition of autocrine and/or endocrine growth factors.

The optimal dose of the analogue is not yet clear. We have used a relatively low dose compared with others, and higher doses might improve the results. We attempted higher doses in some of our patients, and they tolerated these doses well (100 μg/h intravenously). SMS 201-995 has relatively few adverse effects. The occurrence of steatorrhea, an observed side effect in other reports (29), was not thoroughly studied in this patient material. Hypocalcemia, attacks of cholangitis, and the worsening of hypoglycemia seen in the insulinoma patient deserve mention.

In conclusion, the analogue seems to have dual effects, acting both directly on tumor-produced peptide release and indirectly on the peripheral target organs of the peptides. Even though some patients do not respond objectively to the treatment, there may be a beneficial and ameliorating effect on peptide-related symptoms, which is an important goal in the treatment of this patient category. In the management of patients with malignant endocrine pancreatic tumors, SMS 201-995 will probably be a valuable complement to chemotherapy and interferon treatment, especially in acute stages of the disease and in elderly, weak patients because of its very few side effects.

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